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(54) Title: PROCESS FOR THE PREPARATION OF AMORPHOUS CALCIUM SALT OF ATORVASTATIN

(57) Abstract: Present invention refers to the process of preparing amorphous atorvastatin calcium without intermediate isolation of crystal or undefined mixture of crystal and amorphous atorvastatin calcium, respectively. Forming of calcium atorvastatin salt is carried out in a mixture of chlorinated organic solvent or cyclic hydrocarbon solvent, respectively, the non-hydroxylic organic solvent, and water, the source of calcium ions is calcium acetate or calcium chloride, respectively.

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Lek Pharmaceuticals d.d.

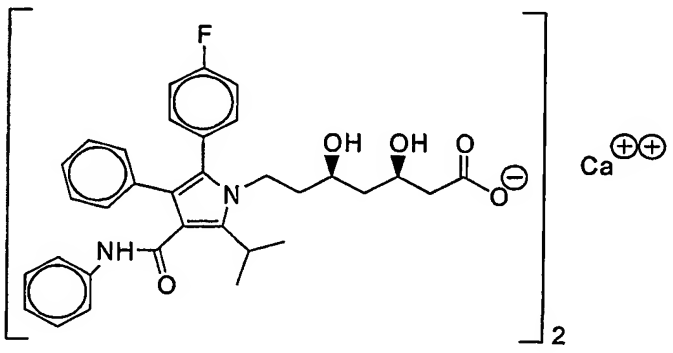
Process for the preparation of amorphous calcium salt of atorvastatin

Field of the Invention

Present invention relates to the field of organic synthesis, more exactly, it relates to the manufacturing process for preparing pharmaceutically acceptable salt of atorvastatin in amorphous form. In a technologically simple way, the invention enables the preparation of amorphous atorvastatin calcium without intermediate isolation of solid crystalline atorvastatin calcium.

Prior Art

Atorvastatin calcium, a substance with chemical name of hemicalcium salt (R-(R*,R*))-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4((phenylamino)carbonyl)-1H-pyrol-1-heptanoic acid and with the chemical formula



is known as inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), that is an enzyme catalyzing the intracellular synthesis of cholesterol. Thus the HMG-CoA reductase inhibitors are especially applicable at treating hypercholesterolemia and hyperlipidemia.

The substance atorvastatin was first described in U.S. Patent 4,681,893 with a generic formula, its salt atorvastatin calcium, however, having been first disclosed in U.S. Patent 5,273,995. Processes for preparing atorvastatin, salts thereof and key intermediates have been described in several patent applications, such as international publications WO 89/07598, WO 92/06968, WO 93/07115, WO 94/20492. As active pharmaceutical substance atorvastatin, usually in the form of a calcium salt, is present in the pharmaceutical form, such as tablets, capsules, powders, and other forms of oral application of medicament.

Atorvastatin calcium may exist in different crystal forms described in different patent applications, such as international publications WO 97/03958, WO 97/03959, WO 01/36384, WO 02/41834, WO 02/43732, WO 02/51804, WO 02/57229, WO 03/004470. The great number of known crystal forms of atorvastatin calcium indicates the fact that the substance is more or less stable in several polymorphous forms.

It is known that atorvastatin calcium obtained by different manufacturing processes is precipitated as low crystalline solid substance having a poorly defined structure. A consequence thereof are relatively badly repeatable processes for preparing the final substances with regard to the polymorphous form, *i.e.*, pharmaceutical active substances prepared in this way are not suitable to be incorporated into pharmaceutical forms, which require strict repeatability in regard to the polymorphous form of active substance.

Processes of preparing amorphous atorvastatin calcium have been disclosed in different patent applications, such as WO 97/03960, WO 00/71116, WO 01/28999, WO 01/42209, WO 02/057228, WO 03/018547. These processes proceed over previously isolated crystal atorvastatin calcium, or an undefined mixture of crystal and amorphous atorvastatin calcium. Isolation of substance in crystalline or non-crystalline form and further amorphization represent a two-step synthesis process, which lowers the yield process as a whole.

Processes of preparing non-crystal atorvastatin calcium without intermediate isolation of solid product have been disclosed in international applications WO 01/72706, WO 02/059087, WO 02/083638 and WO 02/083637. Said amorphous forms are not entirely amorphous, these being structures with crystallization nuclei, which in different references are characterized as amorphous. In international patent application WO 03/018547 there is disclosed a process for preparing amorphous atorvastatin calcium with aqueous alkaline or earth alkaline metal bases with advantageous use of calcium hydroxide.

It is known that the amorphous form of an individual pharmaceutical active substance has different dissolution characteristics and a different bioavailability in comparison to crystalline forms (Konno T., Chem. Pharm. Bull., 1990, 38:2003-2007). For some therapeutical indications, bioavailability is one of the key parameters at determining the forms of the pharmaceutical active substance entering the pharmaceutical form. It is generally known that pharmaceutical active substances in amorphous form are better soluble, or dissolve more quickly than crystalline ones. An advantage of amorphous pharmaceutical active substance over crystalline one is especially distinct at poorly soluble substances, such as, *e.g.*, atorvastatin calcium, which is expressed in a higher biological applicability of the active substance.

Short Description of the Drawings

Fig. 1 shows an X-ray powder diffractogram of atorvastatin calcium salt obtained by the process according to Example 1.

Fig. 2 shows an X-ray powder diffractogram of atorvastatin calcium salt obtained by the process according to Example 2.

Fig. 3 shows an X-ray powder diffractogram of atorvastatin calcium obtained by the process according to the preparation Example 3.

Fig. 4 shows an X-ray powder diffractogram of atorvastatin calcium obtained by the process according to Example 4.

Fig. 5 shows an X-ray powder diffractogram of atorvastatin calcium obtained by the process according to Example 5.

Description of the Invention with Examples

In view of above-mentioned advantages of amorphous atorvastatin, such as better bioavailability and better solubility, there is present a constant need to prepare amorphous atorvastatin calcium in one step without isolation of the intermediate solid product, which essentially contributes to lowering the production cost. We have ascertained that the key factor in this process is the selection of the organic solvent used in the step of forming calcium salt of atorvastatin, *i.e.*, prior to precipitation thereof. We found out that atorvastatin calcium is very well soluble in mixture of chlorinated organic solvents selected from the group consisting of chloroform, dichloromethane, trichloroethane, or tetrachloroethane and a non-hydroxylic organic solvent, such as *e.g.*, tetrahydrofuran and water. Additionally surprisingly we have found that atorvastatin calcium in spite of its ionic nature is well soluble in a mixture of cyclic hydrocarbon solvent selected from the group consisting of cyclohexane, cyclopentane or methyl cyclohexane and non-hydroxylic organic solvent, such as, *e.g.*, tetrahydrofuran, and water.

Especially advantageous is the fact that in said mixture of solvents the substance is better soluble than in a water solution. Consequently, in the step of preparing calcium salt of atorvastatin with the aid of an inorganic source of calcium ions, a systems of solvents may be used – a chlorinated organic solvent/an organic non-hydroxylic solvent/water or a cyclic hydrocarbon solvent/an organic non-hydroxylic solvent/water, without precipitation having taken place of less soluble compounds, such as calcium inorganic salts and sodium salt of atorvastatin, which ensures from alkalization of the reaction mixture with sodium hydroxide.

The main object of the present invention is, consequently, to prepare an amorphous form of atorvastatin calcium without intermediate isolation or precipitation, respectively, of crystalline or undefined mixture of crystalline and amorphous atorvastatin calcium. This object is attained in that the formation of atorvastatin calcium salt is carried out in solvent mixtures, namely, solvent mixture of chlorinated organic solvent and an organic non-hydroxylic solvent and water or solvent mixture of cyclic hydrocarbon solvent and an organic non-hydroxylic solvent and water.

In the step of formation of calcium salt of atorvastatin no precipitation of calcium or any other salt of atorvastatin takes place. Chlorinated organic solvents or cyclic hydrocarbon solvents may be used in quantities which in a mixture with an organic non-hydroxylic solvent and water ensure total solubility of all components until the last synthesis step when atorvastatin calcium salt precipitates from the solution with an addition of solvent in which the product is low soluble, or is insoluble, respectively.

Different calcium sources may be used for the preparation of calcium salt of atorvastatin, as for example water solution of calcium acetate or calcium chloride, respectively. The present invention can use calcium acetate or calcium chloride. Namely, by using some of other calcium sources, such as, *e.g.*, calcium hydroxide, it is necessary before the precipitation of atorvastatin from the organic solvents mixture to filtrate the mixture due to the circumstance that calcium hydroxide is less soluble in chlorinated organic solvents in comparison to calcium acetate. An additional disadvantage of presence of calcium hydroxide in the reaction mixture with the chlorinated organic solvent or cyclic hydrocarbon solvents is in the appearance of reaction mixture turbidity, which effects on the forming of the desired amorphous atorvastatin and the amount of impurities present in the final product, as well. In this case the product should, for use in a pharmaceutical formulation, be additionally purified.

A further object of the present invention is the preparation of amorphous form of atorvastatin calcium according to the process, which includes the following steps:

a) Preparation of a neutral reaction mixture containing sodium salt of atorvastatin, which is dissolved in a mixture of non-hydroxylic organic solvent, such as, *e.g.*, tetrahydrofuran, and water in an 8:1 ratio. The obtained reaction mixture shows a pH in the range between 6.5 and 8.0.

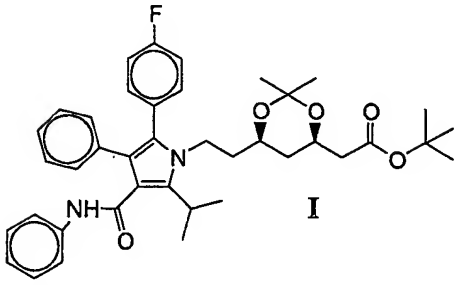
b) To the obtained solution there is added a onefold to a fivefold volume with respect to the existing volume of chlorinated organic solvent selected from the group consisting of dichloromethane, tetrachloroethane, trichloroethane, chloroform, preferably chloroform or cyclic hydrocarbon solvent selected from the group consisting of cyclohexane, cyclopentane or methyl cyclohexane, preferably cyclohexane, and 0.5fold to a twofold volume of saturated water solution of sodium chloride with respect to the existing volume. Optionally in case chlorinated organic solvents are used and necessary in case cyclic hydrocarbon solvents are used, both organic and water layer are separated in a funnel separator. After the separation the organic layer is saved for further use in the preparation process.

c) To the reaction mixture of previously prepared sodium salt of atorvastatin an equivalent or an excess quantity of calcium ions source is added. As source of calcium ions, water solution of calcium acetate or calcium chloride, preferably calcium acetate is used. The product atorvastatin calcium salt is formed in the solution.

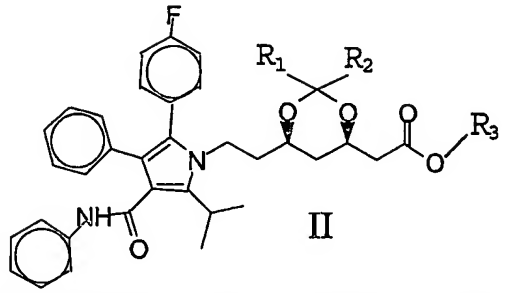
d) Isolation of atorvastatin calcium salt proceeds according to hitherto known and disclosed processes.

An object of the present invention is also the preparation of amorphous form of atorvastatin calcium from the compound of formula I or II without intermediate isolation of crystal or undefined mixture of crystal and amorphous atorvastatin calcium. An advantage of this process is that it assures a pharmaceutical quality of the final product without special additional purification of the obtained substance.

According to the process, which is object of present invention, the compound with the formula I or II



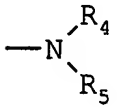
I



II

dently repr e carbon atoms, phenyl, or R_1 in R_2 are taken together as $(-CH_2)_n-$, wherein n may be 4 or 5; R_3 may represent straight or branched chain alkyl of from one to eight carbon atoms or cycloalkyl of from three to six carbon atoms, R_3 may represent tert-butyl, tert-amyl or α,α-dimethylbenzyl.

Group $-O-R_3$ may be substituted by the group with the formula:



wherein R_4 and R_5 may independently represent

- alkyl with one to ten carbon atoms,
- cyclopropyl,
- cyclobutyl,
-cyclopentyl,
- cyclohexyl,
- benzyl or phenyl,

or R_4 in R_5 are taken together to form:

$-(CH_2)_4-$,

$-(CH_2)_5-$,

$-(CH(R^6)-CH_2)_3-$,

$-(CH(R^6)-CH_2)_4-$,

$-(CH(R^6)-(CH_2)_2-CH(R^6))-$,

$-(CH(R^6)-(CH_2)_3-CH(R^6))-$,

$-CH_2-CH_2-O-CH_2-CH_2-$,

$-CH(R^6)-CH_2-O-CH_2-CH_2-$,

$-CH(R^6)-CH_2-O-CH_2-CH_2(R^6)-$,

wherein R^6 represents alkyl with one to four carbon atoms,

is dissolved in a non-hydroxylic solvent, such as, *e.g.*, tetrahydrofuran.

The obtained solution is acidified and stirred at a temperature between 5 and 40 °C, preferably at room temperature until it is by thinlayer chromatography no longer possible to detect the starting compounds with the formula I or II. Subsequently, to the solution a base such as, *e.g.*, NaOH is added, until the pH of the solution does not reach a value between 8.0 and 14.0, preferably between 9.0 and 12.0. The obtained solution is mixed at temperature between 5 and 40 °C, preferably at room temperature. To the reaction mixture, under intense stirring, an acid is cautiously added until the pH is not in the range between 6.5 and 8.0, preferably 7.8. The formed reaction mixture contains sodium salt of atorvastatin.

To the obtained solution there is added with respect to its existing volume a onefold to a fivefold volume of chlorinated organic solvent selected from the group consisting of dichloromethane, trichloroethane, tetrachloroethane, chloroform, preferably chloroform or cyclic hydrocarbon solvent selected from the group consisting of cyclohexane, cyclopentane, and methyl cyclohexane, and a 0.5fold to a twofold volume of saturated aqueous solution of sodium chloride with respect to the existing volume. If the cyclic hydrocarbon solvent is used the resulted layers are separated in a funnel separator. The organic layer is saved for further reaction process.

To the reaction mixture or to the organic layer from the separation process an equivalent quantity of calcium ions or excess thereof is added. As source of calcium ions, aqueous solution of calcium acetate or calcium chloride, preferably calcium acetate, is used. To the organic phase of the obtained two-phase system a drying agent, such as, *e.g.*, magnesium sulphate, is added, which is later on removed by filtration. The reaction mixture is further on concentrated to a threshold value when

the concentrate is still entirely clear, and during this process, however, the solution must always be entirely clear.

Optionally afterwards the reaction mixture is concentrated to about half of initial volume or a threshold value when the concentrate is still entirely clear, during this process, however, the solution must always be entirely clear. After that twofold of concentrated mixture volume is added a solvent in which atorvastatin is well soluble, *i.e.*, *e.g.*, methanol, ethanol or propanol, and which mixes with used chlorinated organic solvent or cyclic hydrocarbon and a portion of an active coal is also added to the said concentrated mixture. Reaction mixture is mixed for about one hour and filtered. The reaction mixture is further concentrated to a threshold value when the concentrate is still entirely clear, during this process, however, the solution must always be entirely clear.

To the obtained concentrate optionally a twofold up to a sixfold, preferably a threefold, volume of solvent is added to its existing volume, The solvent is such that in which atorvastatin is well soluble, *i.e.*, *e.g.*, methanol, ethanol or propanol, and which is capable of mixing with used chlorinated organic solvent or cyclic hydrocarbon solvent according to the present invention and as well with the solvent used in the next step for precipitating atorvastatin calcium. The reaction mixture is then concentrated to a threshold when the concentrate is still entirely clear, and during this process, however, the solution must always be entirely clear.

Subsequently, a 0.4fold to a 0.8fold volume of solvent with regard to the existing volume of solution, preferably a 0.4fold volume of solvent, in which atorvastatin calcium is not soluble, or is low soluble, is optionally added. As solvent, ether, preferably diisopropyl ether, may be used. The reaction mixture prepared in such a way is under intense stirring poured into a fourfold to eightfold volume of the same solvent with regard to the existing volume, preferably fivefold volume of the same solvent. The reaction mixture is stirred at a temperature from 10 to 30 °C, preferably at room temperature. In this step a precipitate of final product - amorphous atorvastatin calcium salt is formed. After removing the solvent by filtration, optionally digerating the product with the organic solvent in which atorvastatin calcium salt is

not soluble or is low soluble and washing the product on the filter, final product amorphous atorvastatin calcium salt is dried in vacuum at a temperature from 35 to 45 °C.

A further object of the present invention is a pharmaceutical composition and form containing amorphous atorvastatin calcium obtained according to the present invention, and pharmaceutically acceptable additives. An advantage of atorvastatin calcium obtained according to the present invention lies in that prior to application in pharmaceutical industry, the active substance need not be additionally purified. The pharmaceutical form may cover tablets, capsules, powders, bags, syrups or suspensions for oral, parenteral, rectal, transdermal or nasal application. The pharmaceutical form may be prepared according to conventional processes known in prior art.

Amorphous atorvastatin calcium prepared according to the present invention is used for preparing medicaments for the treatment of diseases selected from the group consisting of dislipidemia, hyperlipidemia, hypercholesterolemia, aterosclerosis, arteriosclerosis, cardiovascular diseases, coronary arterial diseases, coronary heart diseases, disorders of blood circulation, inflammation diseases, bone diseases, disorders of processing beta amyloid precursor protein, such as Alzheimer's disease or Down's syndrome.

The present invention is illustrated by the following examples. Although these examples are illustrative, they are not intended to be limiting.

Example 1.

4.37 g tert-butyl (6-{2-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoylpyrol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetate are dissolved in 35 ml tetrahydrofuran, then 5 ml 10 % hydrochloric acid are added, and the solution is stirred at room temperature for 15 hours. 1.2 g solid sodium hydroxide is added, and it is stirred for further 3 hours. pH of the reaction mixture is

set to 7.8 with 5N hydrochloric acid at room temperature. To the obtained solution, 50 ml chloroform and 25 ml saturated solution of sodium chloride are added.

To this solution under intense stirring is added a solution of 0.76 g $Ca(OAc)_2.H_2O$ in 10 ml water. The obtained two-phase system is stirred for 30 minutes at 30 °C, and the layers are separated. The organic phase is dried with magnesium sulphate and concentrated. To the clear concentrate, methanol is added, and the mixture is once again concentrated.

To the clear concentrate, 5 ml diisopropylether are added. The obtained solution is under intense stirring added into 100 ml diisopropylether. It is stirred for 1 hour and filtrated, after that precipitate is digerated with 50 ml ether, filtrated and the precipitate is on the filter washed with three times 10 ml ether each. The precipitation is dried in vacuum of about 1 mbar at 45 °C overnight.

Obtained are 3.74 g amorphous calcium salt of atorvastatin.

Example 2.

4.37 g tert-butyl (6-{2-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoylpyrol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetate are dissolved in 35 ml tetrahydrofuran, then 5 ml 10 % hydrochloric acid are added and the solution is stirred at room temperature for 15 hours. 1.2 g solid sodium hydroxide is added, and it is stirred for further 3 hours. pH of the reaction mixture is set to 7.8 with 5N hydrochloric acid at room temperature. To the obtained solution, 100 ml dichloromethane and 25 ml saturated solution of sodium chloride are added.

To this solution there is under intense stirring added a solution of 0.76 g $Ca(OAc)_2.H_2O$ in 10 ml water. The obtained two-phase system is stirred for 1 hour at 30 °C, and the layers are separated. The organic phase is dried with magnesium sulphate and concentrated.

To the clear concentrate, 5 ml diisopropylether are added. The obtained solution is under intense stirring added into 100 ml diisopropylether. It is stirred for 1 hour and filtrated, after that precipitate is digerated with 50 ml ether, filtrated and the precipitate is on the filter washed with three times 10 ml ether each. The precipitate is dried in vacuum of about 1 mbar at 45 °C overnight.

Obtained are 3.09 g amorphous calcium salt of atorvastatin.

Example 3.

4.37 g tert-butyl (6-{2-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoylpyrol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetate are dissolved in 35 ml tetrahydrofuran, then 5 ml 10 % hydrochloric acid are added, and the solution is stirred at room temperature for 15 hours. 1.2 g solid sodium hydroxide is added, and it is stirred for further 3 hours. pH of the reaction mixture is set to 7.8 with 5N of hydrochloric acid at room temperature. To the obtained solution, 50 ml chloroform and 25 ml saturated solution of sodium chloride are added.

To this solution there is under intense stirring added a solution of 0.632 g $CaCl_2.2H_2O$ in 10 ml water. The obtained two-phase system is stirred for 30 minutes at 30 °C, and the layers are separated. The organic phase is dried with magnesium sulphate and concentrated.

To the clear concentrate, 5 ml diisopropylether are added. The obtained solution is under intense stirring added into 100 ml diisopropylether. It is stirred for 1 hour and filtrated, after that precipitate is digerated with 50 ml ether, filtered and the separated precipitate is on the filter washed with three times 10 ml ether each. The precipitate is dried in vacuum of about 1 mbar at 45 °C overnight.

Obtained are 3.65 g amorphous calcium salt of atorvastatin.

Example 4.

8.74 g tert-butyl (6-{2-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoylpyrol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetate are dissolved in 70 ml tetrahydrofuran, then 10 ml 10 % hydrochloric acid are added and the solution is stirred at room temperature for 15 hours. 2.4 g solid sodium hydroxide are added, and it is stirred for further 3 hours. pH of the reaction mixture is set to 7.8 with 5N hydrochloric acid at room temperature. To the obtained solution, 70 ml cyclohexane and 30 ml saturated water solution of sodium chloride are added. The layers are separated.

To the organic phase, under intensive stirring, a solution of 1.52 g $Ca(OAc)_2.H_2O$ on 20 ml water is added. The obtained two-phase system is stirred for 1 hour at 30 °C, and the layers are separated. The organic phase is dried with $MgSO_4$, $MgSO_4$ is filtered off and the mixture is vaporized to a volume of about 60 ml.

The obtained solution is under intensive stirring added into 200 ml diisopropyl ether. It is stirred for 1 hour and filtrated, precipitate is digerated with 100 ml diethyl ether, filtrated and the precipitate is on the filter washed with three times 20 ml diethyl ether each. The precipitate is dried in a vacuum about 1 mbar at 45 °C overnight.

Obtained are 7.08 g amorphous calcium salt of atorvastatin.

Example 5.

8.47 g tert-butyl (6-{2-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoylpyrol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetate are dissolved in 70 ml tetrahydrofuran, then 10 ml 10 % hydrochloric acid are added, and the solution is stirred at room temperature for 15 hours. 2.4 g solid sodium hydroxide are added, and it is stirred for further 3 hours. pH of the reaction mixture is set to 7.8 with 5N hydrochloric acid at room temperature. To the obtained solution, 70 ml cyclohexane, and 30 ml saturated water solution of sodium chloride are added. The layers are separated.

To the upper layer is under intense stirring added a solution of 1.52 g $Ca(OAc)_2.H_2O$ in 20 ml water. The obtained two-phase system is stirred for 1 hour at 30 °C, and the layers are separated.

The organic phase is dried with $MgSO_4$, $MgSO_4$ is filtrated off and the residue is evaporated to a volume about 50 ml, then 100 ml methanol and 0.874 g of active coal is added. The mixture is stirred for 1 hour, and active coal filtrated off. The mixture is concentrated to a volume of about 20 ml.

To the clear concentrate, 10 ml diisopropylether are added. The obtained solution is under intense stirring added into 200 ml diisopropylether. It is stirred for 1 hour and filtrated, then precipitate is digerated with 100 ml diethyl ether, filtered and the precipitate is on the filter washed with three times 20 ml diethylether each. The precipitate is dried in vacuum of about 1 mbar at 45 °C overnight.

Obtained are 5.83 g amorphous calcium salt of atorvastatin.

The obtained samples of amorphous atorvastatin calcium salt were analyzed with X-ray powder diphraction analysis, and exhibit X-ray powder diffractograms shown in Figs. 1 to 5.

The X-ray powder diffraction pattern was collected on a Philips PW1710 diffractometer in reflection geometry. The instrument was regularly calibrated with silicon standard. A standard Philips back-loading sample holder was used. Sample storage, mounting, and data collection were performed at room temperature. Instrumental parameters were: CuK_α radiation (30 mA, 40 kV, λ = 1.5406 Å, variable divergence slit (approx. 12 × 16 mm irradiated area), 0.4 mm receiving slit, graphite monochromator on the secondary side, scintillation counter. Data collection parameters were: 2θ range from 4 ° to 37 °, step scan mode in steps of 0.04 ° 2θ, integration time 1 second at each step.

CLAIMS

1. A process for the preparation of amorphous atorvastatin calcium, which comprises preparation of calcium salt of atorvastatin in a mixture of solvents consisting of a chlorinated organic solvent, a non-hydroxylic organic solvent, and water and at which the source of calcium ions is selected from the group consisting of calcium acetate and calcium chloride.

2. A process for the preparation of amorphous atorvastatin calcium, which comprises preparation of calcium salt of atorvastatin in a mixture of solvents consisting of a cyclic hydrocarbon solvent, a non-hydroxylic organic solvent, and water and at which the source of calcium ions is selected from the group consisting of calcium acetate and calcium chloride.

3. A process for the preparation of amorphous atorvastatin calcium according to claim 1, characterized in that the chlorinated organic solvent is selected from the group consisting of chloroform, trichloroethane, dichloromethane and tetrachloroethane.

4. A process for the preparation of amorphous atorvastatin calcium according to claim 3, characterized in that the chlorinated organic solvent is chloroform.

5. A process for the preparation of amorphous atorvastatin calcium according to claim 3, characterized in that the chlorinated organic solvent is dichloromethane.

6. A process for the preparation of amorphous atorvastatin calcium according to claim 2, characterized in that the cyclic hydrocarbon solvent is selected from the group consisting of cyclohexane, cyclopentane and methyl cyclohexane.

7. A process for the preparation of amorphous atorvastatin calcium according to claim 6, characterized in that the cyclic hydrocarbon solvent is cyclohexane.

8. A process for the preparation of amorphous atorvastatin calcium according to claim 6, characterized in that the cyclic hydrocarbon solvent is cyclopentane.

9. A process for the preparation of amorphous atorvastatin calcium according to claim 6, characterized in that the cyclic hydrocarbon solvent is methyl cyclohexane.

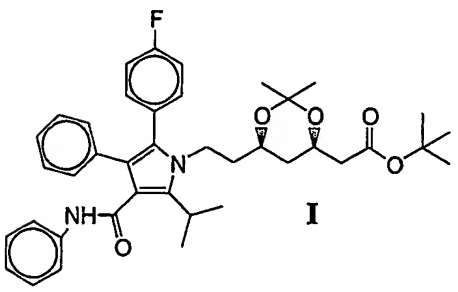
10. A process for the preparation of amorphous atorvastatin calcium according to claims 1 and 2, characterized in that the non-hydroxylic organic solvent is tetrahydrofuran.

11. A process for the preparation of amorphous atorvastatin calcium which comprises:

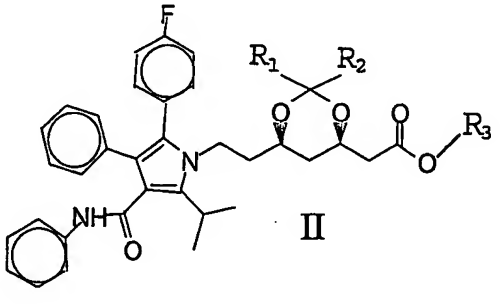
a) preparation of a neutral reaction mixture containing sodium salt of atorvastatin,
b) addition of chlorinated organic solvent selected from the group consisting of dichloromethane, trichloroethane, tetrachloroethane and chloroform, or addition of cyclic hydrocarbon solvent selected from the group consisting of cyclohexane, cyclopentane, and methyl cyclohexane,
c) addition of an equivalent or an excess quantity of calcium ions source selected from the group consisting of calcium acetate and calcium chloride,
d) isolation of atorvastatin calcium.

12. A process for the preparation of amorphous atorvastatin calcium according to claim 11 characterized in that the neutral reaction mixture comprising atorvastatin sodium salt is prepared by a process which comprises:

a) dissolving a compound of formula I or II



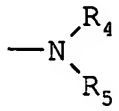
I



II

wherein R_1 and R_2 may independently represent hydrogen, alkyl with one to three carbon atoms, phenyl, or R_1 in R_2 are taken together as $(-CH_2)_n-$, wherein n may be 4 or 5;

R^3 may represent straight or branched chain alkyl of from one to eight carbon atoms or cycloalkyl of from three to six carbon atoms
group -O-R_3 may be substituted by the group with the formula:



wherein R_4 and R_5 may independently represent alkyl with one to ten carbon atoms, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, benzyl or phenyl, or R_4 in R_5 are taken together to form: $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH(R^6)-CH_2)_3-$, $-(CH(R^6)-CH_2)_4-$, $-(CH(R^6)-(CH_2)_2-CH(R^6))-$, $-(CH(R^6)-(CH_2)_3-CH(R^6))-$, $-CH_2-CH_2-O-CH_2-CH_2-$, $-CH(R^6)-CH_2-O-CH_2-CH_2-$, $-CH(R^6)-CH_2-O-CH_2-CH_2(R^6)-$, wherein R^6 represents alkyl with one to four carbon atoms,
in a non-hydroxylic organic solvent
b) preparing sodium salt of atorvastatin in a neutral reaction mixture,

13. A process for the preparation of amorphous atorvastatin calcium according to claim 12, characterized in that a non-hydroxylic organic solvent is tetrahydrofuran.

14. A process for the preparation of amorphous atorvastatin calcium according to claim 11, characterized in that the neutral reaction mixture comprising sodium salt of atorvastatin shows a pH between 6.5 and 8.0.

15. A process for the preparation of amorphous atorvastatin calcium according to claim 11, characterized in that the chlorinated organic solvent is selected from the group consisting of chloroform, trichloroethane, dichloromethane, and tetrachloroethane.

16. A process for the preparation of amorphous atorvastatin calcium according to claim 15, characterized in that the chlorinated organic solvent is chloroform.

17. A process for the preparation of amorphous atorvastatin calcium according to claim 15, characterized in that the chlorinated organic solvent is dichloromethane.

18. A process for the preparation of amorphous atorvastatin calcium according to claim 11, characterized in that the cyclic hydrocarbon solvent is selected from the group consisting of cyclohexane, cyclopentane and methyl cyclohexane.

19. A process for the preparation of amorphous atorvastatin calcium according to claim 18, characterized in that the cyclic hydrocarbon solvent is cyclohexane.

20. A process for the preparation of amorphous atorvastatin calcium according to claim 18, characterized in that the cyclic hydrocarbon solvent is cyclopentane.

21. A process for the preparation of amorphous atorvastatin calcium according to claim 18, characterized in that the cyclic hydrocarbon solvent is methyl cyclohexane.

22. A process for the preparation of amorphous atorvastatin calcium according to claims 11, characterized in that the chlorinated organic solvent or cyclic hydrocarbon solvent is added in a onefold to fivefold quantity with respect to the existing volume of the solution.

23. A process for the preparation of amorphous atorvastatin calcium according to claims 11, characterized in that simultaneously with an addition of the chlorinated organic solvent or cyclic hydrocarbon solvent also a 0.5fold to a twofold quantity of saturated aqueous solution of sodium chloride with respect to the existing volume of the solution is added.

24. A process for the preparation of amorphous atorvastatin calcium according to claim 11, characterized in that the isolation of atorvastatin calcium comprises an addition of solvent in which atorvastatin calcium is poorly soluble.

25. A process for the preparation of amorphous atorvastatin calcium according to claim 24, characterized in that the solvent in which atorvastatin calcium is poorly soluble, is ether.

26. A process for the preparation of amorphous atorvastatin calcium according to claim 25, characterized in that the solvent in which atorvastatin calcium is poorly soluble, is diisopropylether.

27. A process for the preparation of amorphous atorvastatin calcium according to claim 11, characterized in that the isolation of atorvastatin calcium comprises:

a) adding a solvent in which atorvastatin calcium is well soluble,

b) concentrating the obtained mixture,

c) adding a solvent in which atorvastatin calcium is poorly soluble so that it, consequently, separates from the reaction mixture.

28. A process for the preparation of amorphous atorvastatin calcium according to claim 27, characterized in that the solvent in which atorvastatin calcium is well soluble is selected from the group consisting of methanol, ethanol and propanol.

29. A process for the preparation of amorphous atorvastatin calcium according to claim 28, characterized in that the solvent in which atorvastatin calcium is well soluble is methanol.

30. A process for the preparation of amorphous atorvastatin calcium according to claim 27, characterized in that the solvent in which atorvastatin calcium is poorly soluble is ether.

31. A process for the preparation of amorphous atorvastatin calcium according to claim 30, characterized in that the solvent in which atorvastatin calcium is poorly soluble is diisopropylether.

32. Use of amorphous atorvastin calcium, prepared by the process as described in any previous claims from 1 to 31 for the preparation of a medicament for the treatment of diseases selected from the group consisting of dislipidemia, hyperlipidemia, hypercholesterolemia, aterosclerosis, arteriosclerosis, cardiovascular diseases, coronary arterial diseases, coronary heart diseases, disorders of blood circulation, inflammation diseases, bone diseases, disorders of processing beta amyloid precursor protein, such as Alzheimer's disease or Down's syndrome.

33. A pharmaceutical form comprising amorphous atorvastatin calcium prepared by the process as described in any previous claims from 1 to 32, and pharmaceutically acceptable ingredients.

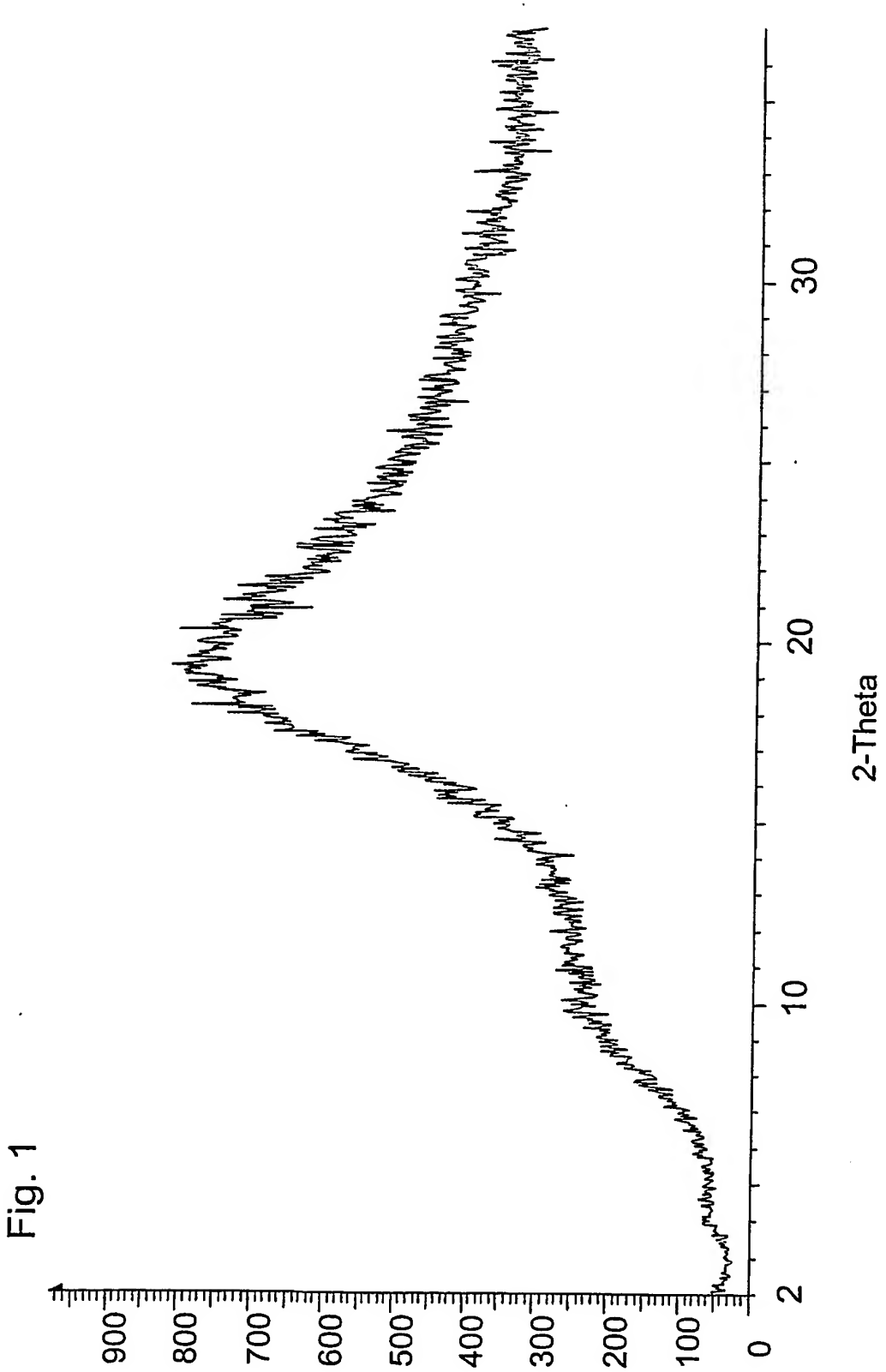


Fig. 1

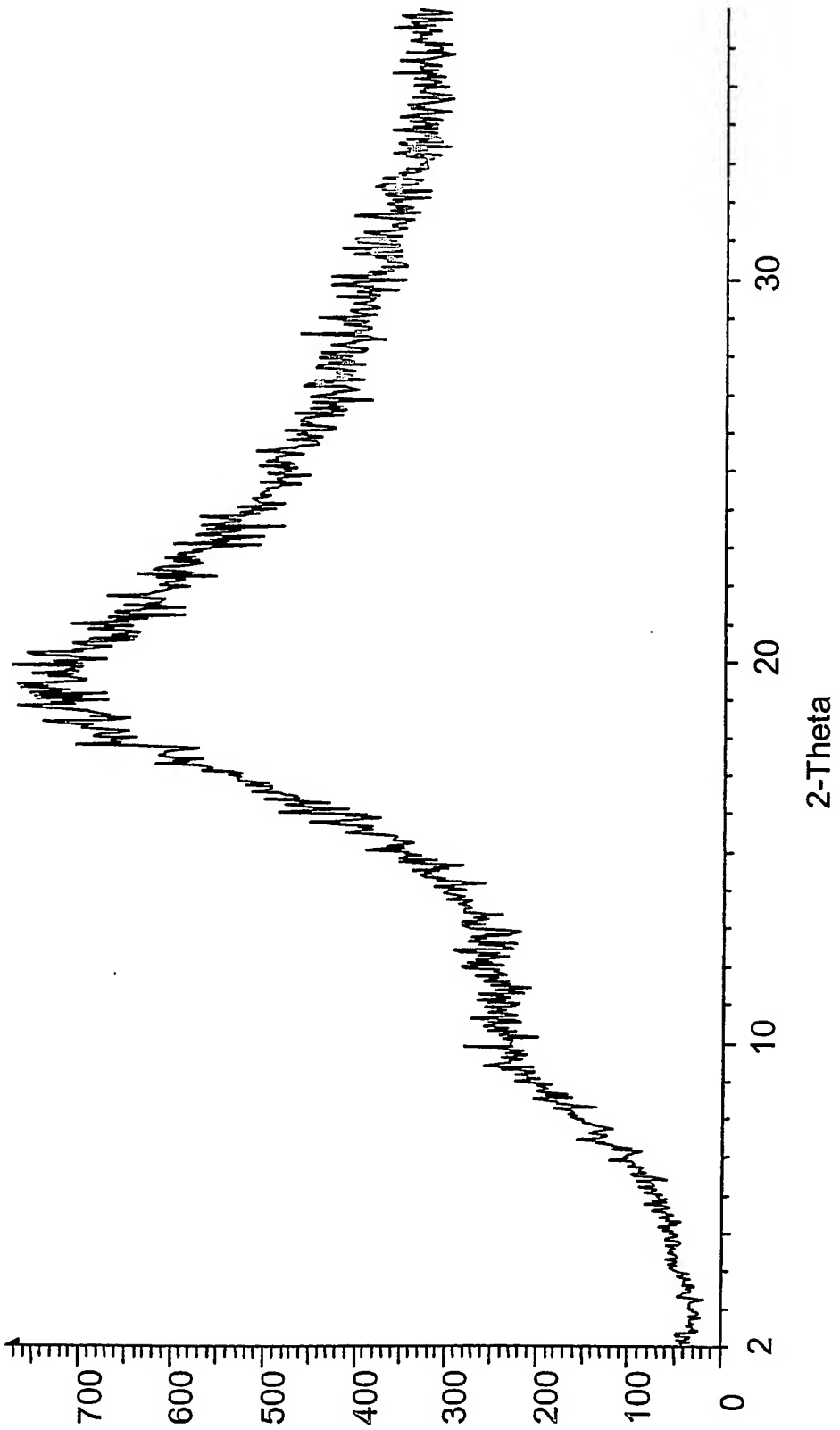


Fig. 2

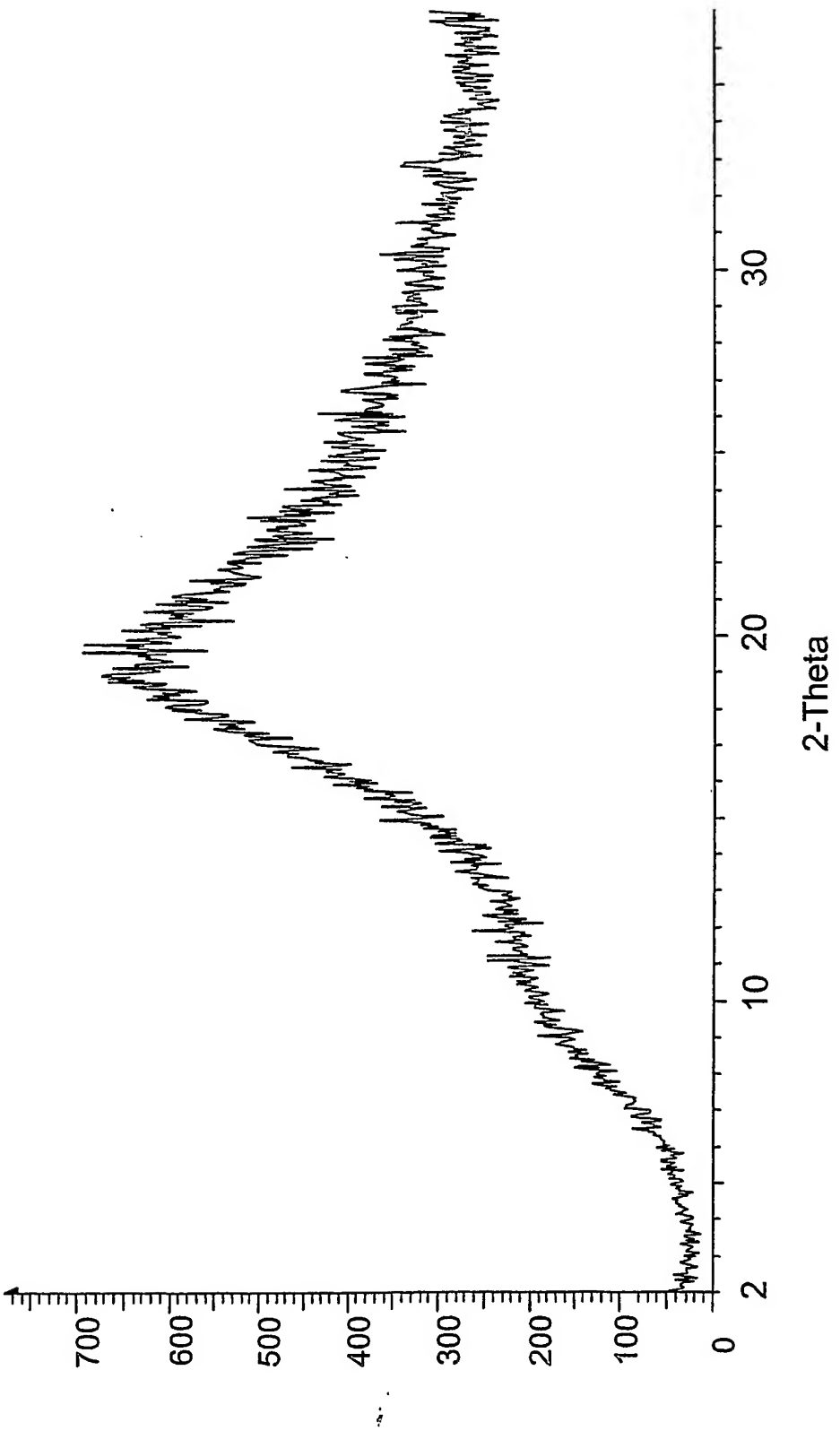


Fig. 3

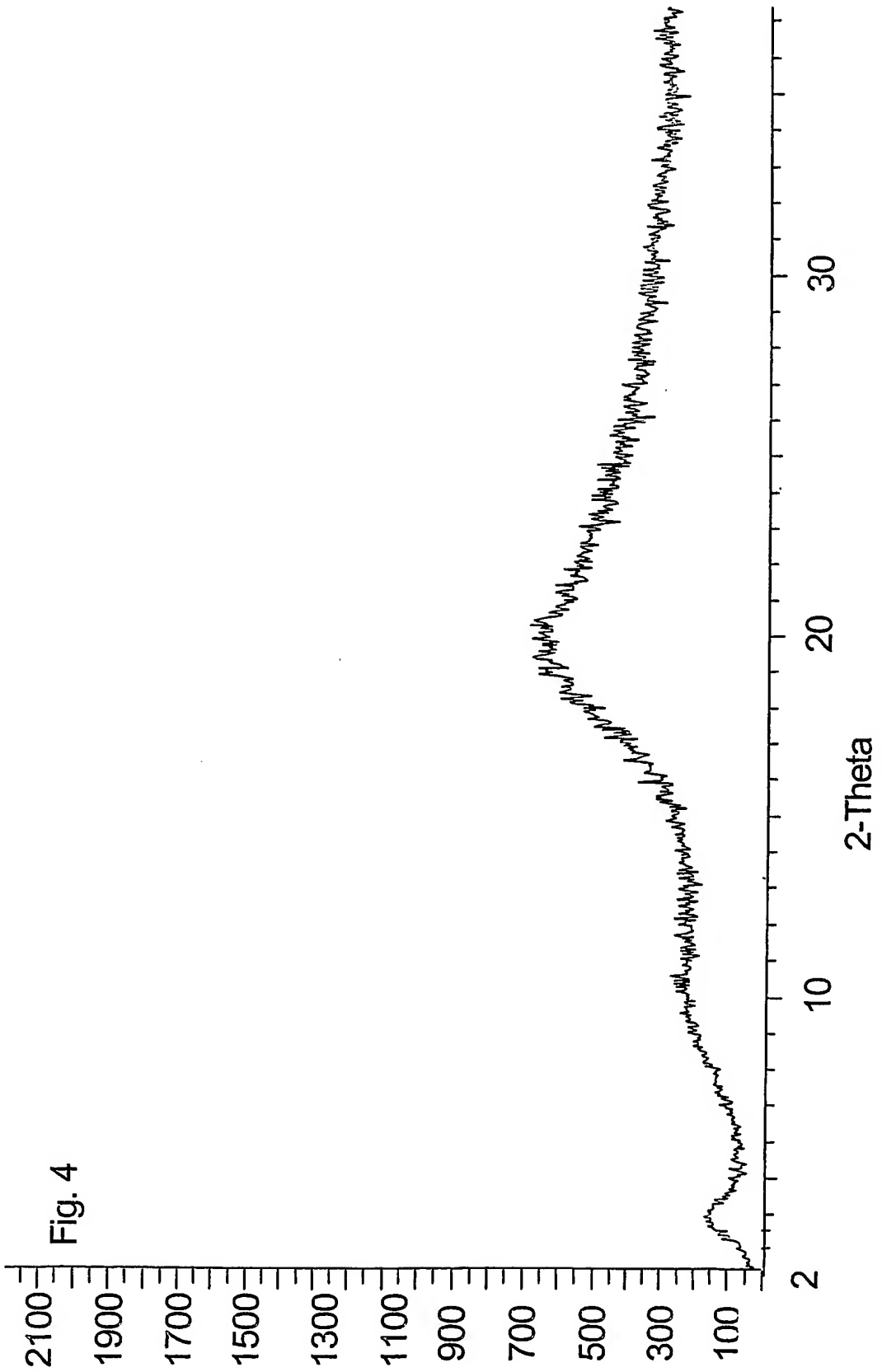

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Fig. 4

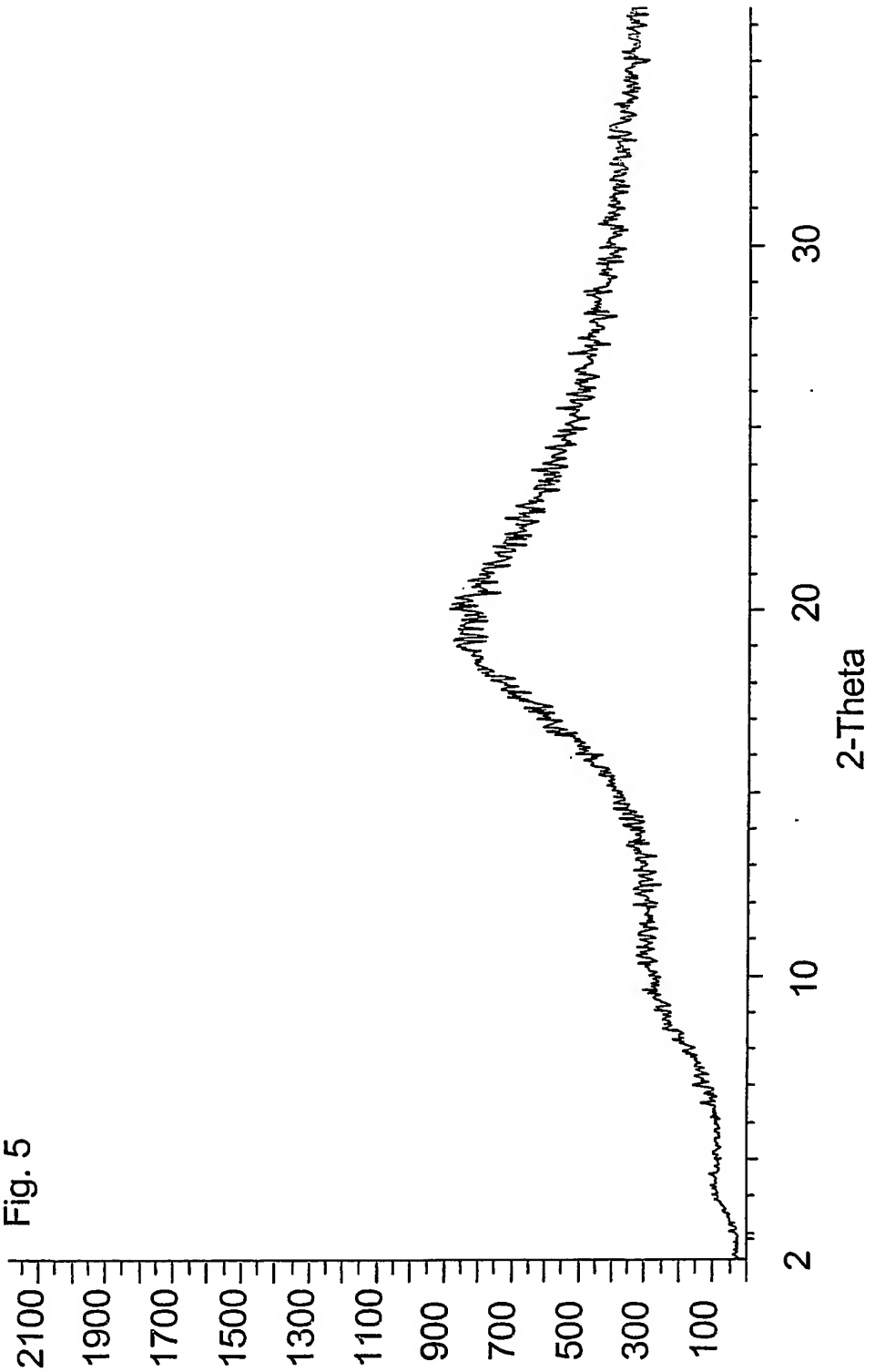
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Fig. 5

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D207/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	page 6, line 18 - page 9, line 18	1,3-9, 11-33
Y	WO 03/018547 A (SARIN G S ; SINGH J (IN); SURI SANJAY (IN); BANSAL B R (IN); MOREPEN L) 6 March 2003 (2003-03-06) cited in the application the whole document	1-33
Y	WO 01/42209 A (LEK TOVARNA FARMACEVTSKIH ; PFLAUM ZLATKO (SI)) 14 June 2001 (2001-06-14) cited in the application the whole document	1-33

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 August 2004	16/08/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Von Daacke, A

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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